Kinetics and Mechanism of a One-step Alternative to the Grignard Reaction

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The kinetics of the ' one-step alternative to the Grignard reaction ' between bromobenzene, benzaldehyde, and lithium have been studied with tetrahydrofuran as solvent. The rate of formation of the product, diphenylmethanol, is first-order in bromobenzene and in lithium surface area, and zero-order in benzaldehyde. The activation energy is 3.42 ± 0.59 kJ mol^{-1}. These data are consistent with a rate-determining step involving intermediate formation of phenyl-lithium by reaction of bromobenzene with lithium. The one-step process has also been employed with organic bromides to synthesise ketones from nitriles and alkylarylhydroxylamines from 2-methyl-2-nitrosopropane. In the former the yields were poorer than from conventional reactions but in the latter yields compared very favourably with those from the Grignard reaction.

ORGANOLITHIUM compounds and Grignard reagents (organomagnesium halides) have many features in common and for many applications, for example the conversion of carbonyl-containing compounds to alcohols, either type of reagent may serve. Traditionally these syntheses have been two-stage reactions: first the preparation of the organometallic reagent, then reaction with the carbonyl compound. The Grignard reaction is, however, a refinement of the older Barbier synthesis [1] in which the carbonyl compound and the halide are added simultaneously to a suspension of magnesium turnings in ether so that the organomagnesium compound is generated *in situ*. While the Grignard reaction is manifestly superior to, and has virtually superseded the one-step Barbier process, it has recently been shown that the Barbier procedure is improved significantly by replacing magnesium with lithium metal.[2] From a practical standpoint this innovation renders the conversion of aldehydes, ketones, and esters to the corresponding alcohols a very simple operation with yields often exceeding those from the analogous Grignard reaction.[2]

Although this simple ' one-step alternative to the Grignard reaction ' as it has been named,[2] appears to be an attractive synthetic procedure, its kinetics, mechanism, and range of applicability have not been studied in detail. The available evidence strongly favours initial reaction of the organic halide with lithium metal to form an organolithium compound which then adds to the carbonyl compound to form the alcoholate. This paper presents the results of kinetic studies which support this mechanism. The reagents employed were benzaldehyde and bromobenzene with tetrahydrofuran (THF) as solvent. The choice of reagents and conditions was restricted by the requirements that the chosen reaction should be comparatively free from side reactions, should proceed at a measurable rate, and should be amenable to analysis.

Included is a brief account of the reaction as applied to the preparation of alkylarylhydroxylamines (or their oxidation products, the nitroxides) from 2-methyl-2-nitrosopropane and to the preparation of ketones from nitriles. The synthesis of nitroxides is of some topical interest as these stable radicals are in vogue as spin-labels and spin-probes in studies of macromolecules.[3] The conversion of nitriles to ketones is scarcely an important synthetic process, but provides a test of the reaction with a more electronegative group than carbonyl. Bromobenzene and n-butyl bromide were the organic halides.

EXPERIMENTAL

Materials.—THF was stored over molecular sieves for a minimum of seven days, refluxed, and distilled over sodium

[1] P. L. Barbier, *Compt. rend.*, 1898, **128**, 110.
[2] P. J. Pearce, D. H. Richards, and N. F. Scilly (a) *Chem. Comm.*, 1970, **18**, 1160; (b) *J. C.S. Perkin I*, 1972, 1655.
[3] See for example A. T. Bullock, G. G. Cameron, and P. M. Smith, *J.C.S. Faraday II*, 1974, 1202.

wire under nitrogen, then stored for 24 h over fresh sodium wire, and used within 48 h.

Bromobenzene (95%) was purified by fractional distillation and the middle fraction, b.p. 155—156°, collected and stored over molecular sieves. Benzaldehyde (AnalaR; 99.5%) was distilled under reduced pressure and stored under nitrogen over molecular sieves. Long periods of storage were avoided with both reagents which were used where practicable within a few days of distillation.

Lithium shot (99.8%) was washed free of liquid paraffin with light petroleum (b.p. 40—60°) and extruded through a die (to give wire of 1.702 mm diam.) into sodium-dried liquid paraffin. The wire was wound on to a glass rod (13 mm diam.), cut into pieces of two revolutions each, washed with dry light petroleum (b.p. 40—60°), and weighed into sodium-dried light petroleum (b.p. 100—120°). The surface area of the lithium was altered as required by varying the length of wire. In one set of experiments the surface area was altered by using another die to give wire 0.927 mm in diameter. In all kinetic runs the wire was extruded immediately before use to minimise surface oxidation.

Apparatus.—Reactions were carried out in the range −35 to 20°, mainly at −20°, and the required reaction temperature was controlled to ±0.5° by means of a methanol–solid CO_2 bath in conjunction with a Jack-o-matic pneumatic jack and a Thermo-watch control manufactured by Instruments for Research and Industry. The reaction vessel was a 500 ml, three-necked flask fitted with a stirrer, dropping funnel, and nitrogen inlet. The reaction rate was found to increase with stirring rate up to *ca.* 300 r.p.m. and remained constant thereafter. A constant stirring rate of 360 r.p.m. was therefore maintained with a Citenco electric motor.

Procedure.—The following example illustrates the procedure. With dry nitrogen passing through the reaction flask THF (200 ml) and lithium wire (1.702 mm diam.; 0.075 mol; surface area 2 253 mm²), roughly dried with filter paper, were added. After stirring for 30 min a mixture of bromobenzene (0.05 mol, 7.85 g), benzaldehyde (0.04 mol, 4.24 g), and THF (20 ml) was added. Following an induction period of *ca.* 1 min, depending on the quantities of reactants used, the lithium surface changed from a dull matt to a light golden sheen and the solution from colourless to pale green. The nitrogen stream was stopped after 5 min and the vessel sealed.

The reaction was stopped at the desired time by filtering the solution into a 250 ml standard flask. On attaining ambient temperature the THF solution was brought up to the mark. A 50 ml portion was withdrawn, the solvent removed under reduced pressure, and the residue hydrolysed with hydrochloric acid (100 ml, 0.5M). The hydrolysate was extracted with ether (2 × 100 ml); in the second extraction sufficient sodium chloride to salt out all the remaining organic compounds from the aqueous phase was added. A third extraction was carried out to check that removal of the organic compounds was complete. The ether extract was then subjected to g.l.c. to determine the concentration of the product, diphenylmethanol.

Analysis of Products.—G.l.c. analyses were conducted on a 2 m × 1/8 in O.D. stainless steel column packed with 2.5% Silicone OV 17 on Chromosorb G (80—20 mesh) in a Perkin-Elmer F11 modular gas chromatograph equipped with a flame ionisation detector. Ethyl cinnamate was used as internal standard and the relative areas of the product and ethyl cinnamate peaks were determined by cutting and weighing. The yield of diphenylmethanol was calculated from a calibration graph which was checked at frequent intervals to correct for any drift in the instrument response. All g.l.c. analyses were done in triplicate.

Preparation of Ketones and Hydroxylamines (or Nitroxides).—THF solvent, lithium, and bromobenzene were prepared as above. 2-Methyl-2-nitrosopropane (MNP) was synthesised and purified as described elsewhere.[4] The other reagents were of the highest purity commercially available. They were dried over molecular sieves and distilled before use.

Ketones from nitriles. Reactions were conducted as described previously [2] at −20° in THF under dry nitrogen. The molar ratio lithium : bromide : nitrile was 6 : 2 : 1; the final concentration of nitrile was 0.16M. The solution of nitrile and bromide in THF was added dropwise to the lithium suspension over 1 h and the reaction was continued for a further 4 h prior to work up. Apart from the benzonitrile–bromobenzene reaction which was analysed by g.l.c., the yields of products were estimated by conversion of the ketone to its 2,4-dinitrophenylhydrazone.

Hydroxylamines (nitroxides). A number of aryl bromides were reacted with MNP and lithium in THF. The following example typifies the procedure. Lithium wire (0.06 mol, 0.42 g) was suspended in THF (75 ml) and the mixture cooled under a stream of dry nitrogen to −70° in a methanol–solid CO_2 bath. After 30 min, a solution of 2-bromomesitylene (0.03 mol, 5.97 g) and MNP (0.015 mol, 1.305 g) in THF (25 ml) was added dropwise with stirring over 30 min. Stirring was continued for a further 6 h after which lithium was filtered off. The solvent was removed under reduced pressure and the residue treated with water (100 ml) and sufficient dilute hydrochloric acid to make the solution just acid to litmus. The hydrolysate was extracted with ether, which was removed under reduced pressure and the residue (crude hydroxylamine) dissolved in benzene (100 ml). The hydroxylamine in solution was oxidised to the nitroxide by shaking with silver oxide (0.129 mol, 3 g). The product was purified by column chromatography on silica gel with benzene as eluant, yielding, on crystallisation from light petroleum, t-butyl mesityl nitroxide as bright red crystals (m.p. 29.0—29.5°). The identity of the product was further checked from its e.s.r. spectrum.

RESULTS AND DISCUSSION

Table 1 summarises the rate data obtained at different reactant concentrations and temperatures.

The yield–time plots are sigmoidal because of the induction period and the later decrease in rate as the reactants are consumed. The sigmoidal shape is most marked when there is an excess of benzaldehyde over bromobenzene (compare runs 1 and 3 in Figure 1). For run 1 the ultimate yield of diphenylmethanol was low and there were significant amounts of a second product which has not been identified. No valid reaction rate can therefore be deduced from this run. With a small excess of benzaldehyde (run 2) this unknown compound accounted for ≤2% of the total yield, and it was not detected in any of the other runs where an excess of bromobenzene was used. The resulting yield–time

[4] A. Calder, A. R. Forrester, and S. P. Hepburn, *Org. Synth.*, 1972, **52**, 77.

curves, exemplified by runs 3, 9, and 11 in Figure 1, show an approximately linear region which was taken as a measure of the reaction rate as quoted in Table 1.

Reaction Order.—The order of reaction with respect to bromobenzene is obtained from Figure 2. The slope of

exposed surface rather than the total mass of lithium. The data for runs 9 and 11 in Figure 1 do not bear out earlier conclusions [2b] that the product yield diminishes with increasing lithium surface area.

From the constancy of the reaction rates in runs 4, 7,

TABLE 1

Rate of formation (k) of diphenylmethanol as a function of reactant concentration and temperature

Run no.	$T/^\circ C$	[Bromobenzene]/M	[Benzaldehyde]/M	$10^{-3} \times$ Li surface area [a] $(mm^2\ l^{-1})$	$10^5 k/mol\ l^{-1}\ s^{-1}$
1	-20	0.100	0.20	11.27	
2	-20	0.15	0.20	11.27	5.67 ± 0.24
3	-20	0.225	0.20	11.27	8.22 ± 0.29
4	-20	0.25	0.20	11.27	8.94 ± 0.31
5	-20	0.30	0.20	11.27	10.74 ± 0.37
6	-20	0.35	0.20	11.27	13.21 ± 0.47
7	-20	0.25	0.15	11.27	8.88 ± 0.31
8	-20	0.25	0.225	11.27	8.88 ± 0.31
9	-20	0.25	0.20	14.08	11.11 ± 0.33
10	-20	0.25	0.20	16.90	13.47 ± 0.35
11	-20	0.25	0.20	22.53	18.31 ± 0.47
12[b]	-20	0.25	0.20	20.44	16.22 ± 0.44
13	-35	0.25	0.20	11.27	8.08 ± 0.32
14	0	0.25	0.20	11.27	10.00 ± 0.28
15	20	0.25	0.20	11.27	11.21 ± 0.24

[a] Including end faces of lithium wire. [b] Using wire of 0.927 mm diam. All other experiments with lithium wire of 1.702 mm diam.

this linear plot, calculated by a computer least-squares program, is 0.978 ± 0.047 (correlation coefficient τ 0.997). A small adjustment applied to each point in Figure 2 to allow for loss of bromobenzene during the induction period makes very little difference to the slope, the corrected value being 0.965 ± 0.051. Within experimental error the reaction is first-order with respect to bromobenzene.

The reaction order with respect to the lithium surface area is also unity as evidenced by the slope of the line in Figure 3 which is 1.027 ± 0.059 (τ 0.9995). In runs 12 and 4 the same mass of lithium was used, but in the former the surface area was greater because of the smaller
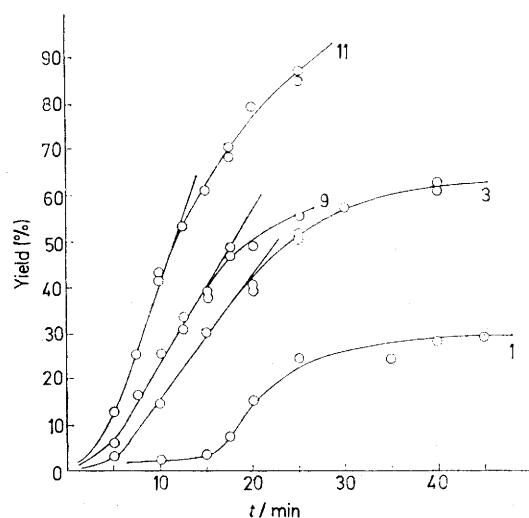
and 8 it is concluded that the reaction is zero-order with respect to benzaldehyde. Therefore, within the concentration range studied the rate equation for the reaction
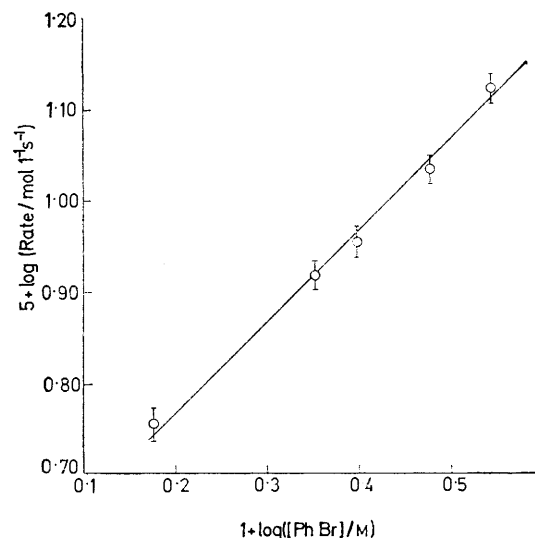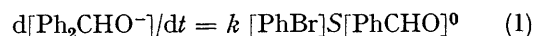

FIGURE 2 log(reaction rate) *versus* log[PhBr] for runs 2—6 of Table 1

is (1) where S is the surface area of the lithium metal. The rate coefficient k is $3.17 \pm 0.11\ l\ mm^{-2}\ s^{-1}$ at -20°.

$$d[Ph_2CHO^-]/dt = k\ [PhBr]S[PhCHO]^0 \qquad (1)$$

Reaction Mechanism.—Equation (1) is consistent with the mechanism in (2) and (3). If step (2) is rate deter-

$$PhBr + Li\ (surface) \xrightarrow{k_1} PhLi + LiBr \qquad (2)$$

$$PhLi + PhCHO \xrightarrow{k_2} Ph_2CHO^-Li^+ \qquad (3)$$

FIGURE 1 Yield of diphenylmethanol as a function of time for runs 1, 3, 9, and 11 of Table 1

diameter of the wire. Comparison of these two runs confirms that the reaction rate is determined by the total
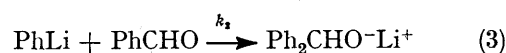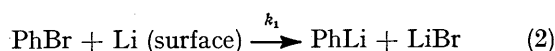
mining then the rate of alcoholate formation is given by equation (4), as observed experimentally. This mechan-

$$\mathrm{d}[Ph_2CHO^-]/\mathrm{d}t = k_1\,[PhBr]S \qquad (4)$$
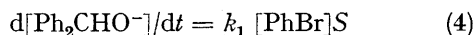
ism is in accord with the earlier suggestion that phenyl-lithium formation is the initial step in the reaction. Other observations support this mechanism. First, benzaldehyde does not react on its own with lithium
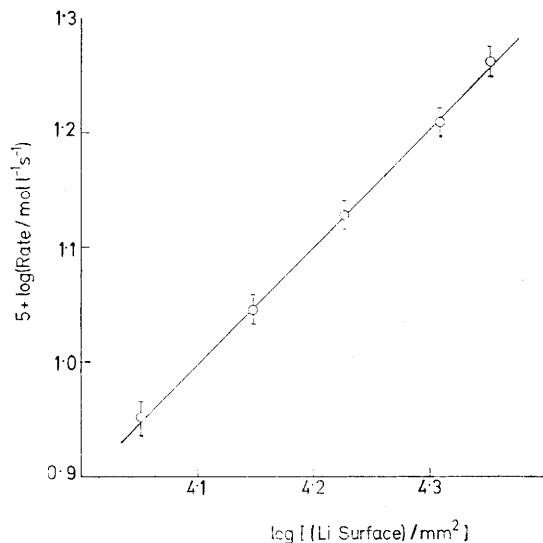

FIGURE 3   log (reaction rate) *versus* log (Li surface area) for runs 4 and 9—12 of Table 1

under the present reaction conditions whilst bromo-benzene readily forms phenyl-lithium. Second, if a polymeric organic halide such as a styrene–*p*-bromosty-rene copolymer is used in place of bromobenzene little or no reaction occurs. This would be expected if steric effects at the lithium surface severely retard formation of the intermediate lithiated polystyrene. *p*-Bromostyrene units can react successfully only when the lithium is in the form of the lithiumnaphthyl complex. On the other hand, a significant proportion of carbonyl groups in poly(methyl vinyl ketone), poly(phenyl vinyl ketone),

TABLE 2

Effect of bromobenzene concentration on induction period [a] (time till appearance of green colour)

[Bromobenzene]/M	t/s [b]
0.10	175
0.15	155
0.225	93
0.25	75
0.30	74
0.35	75

[a] Benzaldehyde 0.20M; Li surface 11.27 × 10³ mm² l⁻¹; temperature −20°. [b] ± 3 s.

and poly(methyl methacrylate) can be converted to alcohol by bromobenzene and lithium in THF.[5] Third, the induction period decreases with increasing bromo-benzene concentration up to a critical limit (Table 2)

⁵ G. G. Cameron, J. M. Elsom, A. J. S. Milton, and N. F. Scilly, unpublished work.

but is unaffected by the benzaldehyde concentration. In this work the induction period depends mainly on the state of the lithium surface; if the wire is not used immediately after extrusion it acquires a heavier oxide coating and the induction period increases. These observations are in line with earlier data on this [2b] and the conventional Grignard reaction.[6] In both cases the induction period can be attributed to initial cleansing of the metal surface by the organic halide. However, impurities such as water in the reagents or solvents could also affect the induction period. Finally, the formation of ketones from nitriles and of hydroxylamines from nitroso-compounds (see below) can be accounted for satisfactorily only on the basis of intermediate organo-lithium formation from the organic halide.

The very low energy of activation, 3.42 ± 0.59 kJ mol⁻¹, from Figure 4 is consistent with a heterogeneous reaction as a rate-determining process. The reaction shown in step (2) is greatly simplified and must be viewed as the overall reaction. Data for comparable reactions are few but it is known that such reactions, which resemble corrosion processes, proceed by a number of steps including diffusion of reactant to surface, absorption of reactant on surface, chemical reaction on surface, desorption of product, and diffusion of product into the bulk medium. The energy of activation depends upon the nature of the rate-controlling process and may have a small positive or negative value. Further understanding of the reaction under consideration would require a detailed study of the attack of alkyl and aryl halides on the lithium surface.
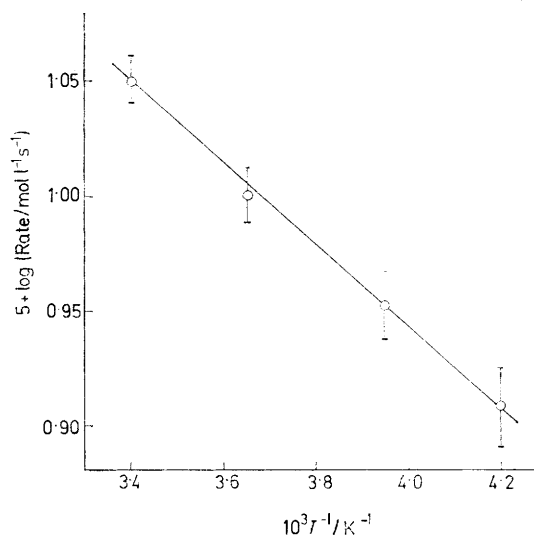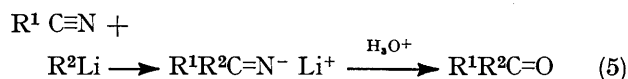

FIGURE 4   Arrhenius diagram for runs 4 and 13—15 of Table 1

Preparative Applications of the Reaction.—Alkyl- and aryl-lithium and Grignard reagents react with the nitrile group to give a ketimine which is hydrolysed to the

⁶ M. Kilpatrick and H. P. Simons, *J. Org. Chem.*, 1938, **2**, 459.

ketone [reaction (5)]. Table 3 summarises the yields

$$R^1 C{\equiv}N +$$

$$R^2Li \longrightarrow R^1R^2C{=}N^- Li^+ \xrightarrow{\text{H}_3\text{O}^+} R^1R^2C{=}O \quad (5)$$

from such reactions studied here. In contrast to carbonyl compounds, nitriles give better yields in conventional reactions than in the one-step procedure where

to nitroxides often occurs spontaneously on exposure to air. Apart from the first system in Table 4, the one-step process gives better yields of alkyl aryl nitroxides than the conventional Grignard reaction. The reason for the failure to obtain a measurable yield of phenyl t-butyl nitroxide is not clear. No attempt was made to optimise reaction conditions but it was observed that when the ratio of 2-bromomesitylene to MNP was reduced from

TABLE 3

Ketone yields from reaction of various nitriles R^2CN and organic bromides R^1Br

R^1	R^2	Product	Yield (%) [a]	Yield (%) from Grignard reaction	Yield (%) from organolithium reaction
Ph	Ph	Benzophenone	64	80 [b,f]	9,[7] 23 [d]
Ph	PhCH$_2$	Deoxybenzoin	3	10 [f] 33 [7]	
Ph	Me	Acetophenone	1	33, 70 [c,g]	36 [h]
Ph	CH$_2$=C–CH$_3$	Phenyl propenyl ketone	2		
Ph	Bu[t]	Phenyl t-butyl ketone	59	72 [b,f]	
Bu[n]	Bu[t]	Phenyl n-butyl ketone	27		
Bu[n]	PhCH$_2$	Benzyl n-butyl ketone	6.5		0, 49 [e,7]

[a] Based on nitrile. [b] Calculated from ketimine formation. [c] Higher yield with Grignard reagent in large excess. [d] Present work. [e] Benzene as solvent. [f] M.S. Kharasch and O. Reinmuth, ' Grignard Reagents of Non-metallic Substances,' Constable, London, 1954. [g] C. R. Hauser and W. J. Humphlett, *J. Org. Chem.*, 1950, **13**, 359. [h] G. Sumrell, *J. Org. Chem.*, 1954, **19**, 817.
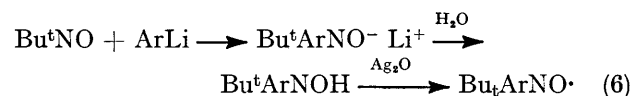
TABLE 4

Nitroxide yields from aromatic bromides (ArBr) and 2-methyl-2-nitrosopropane

Ar	Product	Yield (%) [a]	Yield (%) from Grignard reaction [d]
Ph	Phenyl t-butyl nitroxide	Trace	56 [b]
Me$_3$C$_6$H$_2$	Mesityl t-butyl nitroxide	44	32
p-MeOC$_6$H$_4$	p-Methoxyphenyl t-butyl nitroxide	62 [c]	
p-MeC$_6$H$_4$	p-Tolyl t-butyl nitroxide	37 [b]	38 [b]
Me$_2$C$_6$H$_3$	2,6-Dimethylphenyl t-butyl nitroxide	71	52

[a] Based on MNP. [b] Calculated from hydroxylamine formation. [c] Impure product. [d] A. Calder and A. R. Forrester, *J. Chem. Soc. (C)*, 1969, 1459; A. R. Forrester and S. P. Hepburn, *ibid.*, 1970, 1277.

only benzo- and pivalo-nitriles give reasonable yields. The other nitriles have acidic hydrogen atoms on the carbon α to the cyano-group and probably undergo preferential reaction at that point.[7] In the case of methacrylonitrile the main product (42%) was a polymer containing some reacted nitrile groups.

MNP reacts with aryl lithium compounds [reaction (6)] to yield hydroxylamines after hydrolysis. Oxidation

$$Bu^tNO + ArLi \longrightarrow Bu^tArNO^- Li^+ \xrightarrow{\text{H}_2\text{O}}$$

$$Bu^tArNOH \xrightarrow{\text{Ag}_2\text{O}} Bu_tArNO{\cdot} \quad (6)$$

2 : 1 to 1.2 : 1 the yield fell from 44 to 32%. A similar trend has been observed for the reaction of Grignard reagents with nitroso-compounds.[8]

[7] W. I. O'Sullivan, F. W. Swamer, W. J. Humphlett, and C. R. Hauser, *J. Org. Chem.*, 1961, **26**, 2306.
[8] A. R. Forrester, J. M. Hay, and R. H. Thomson, ' Organic Chemistry of Stable Free Radicals', Academic Press, London, 1968, ch. 5.